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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,604	07/01/2003	Wei Huang	011068-014-999	4803

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 05/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,604	HUANG ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/3/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and response filed February 18, 2005 is acknowledged and entered. The information disclosure statement filed on December 3, 2004 has been considered. Upon further consideration of the instant claims, new grounds are rejection are applied. Any inconvenience is regretted.

Response to Amendments/Arguments

2. The rejection of claims 12, 14, 17 and 19 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's amendments. The rejection of claims 1-19 under 35 U.S.C. 102(b) as being anticipated by Whitcomb (WO 99/61658) is withdrawn in view of Applicant's arguments. The rejection of claims 1-13 and 15-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Richman *et al.* (*J. Virology*, March 1994, 68(3):1660-1666) is withdrawn in view of Applicant's arguments. The rejection of claims 14 and 19 under 35 U.S.C. 103(a) as being unpatentable over Richman in view of Whitcomb (WO 99/61658) is withdrawn in view of Applicant's arguments.

In summary, Applicant argues that the prior art used to reject the claims is directed to drug resistance as a result of various mutations that occur in HIV-1 in response to treatment various reverse transcriptases, rather than the claimed method of determining the replication capacity. Replication capacity of the resistant virus is not taught or suggested in Whitcomb or Richman *et al.* Therefore, the rejections are withdrawn.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9, 11 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by Nijhuis *et al.* (*Current Opinion in Infectious Diseases*, 2001, 14:23-28, "Nijhuis"). The claims are drawn to a method for determining whether an HIV-1 has an increased likelihood of having an impaired replication capacity. A virus has an "increased likelihood of having an impaired replication capacity" if the virus has a property, in this case, a mutation, correlated with an impaired replication capacity. The specification (page 10, lines 27-29) states that, "[A] property of a virus is correlated with an impaired replication capacity if a population of viruses having the property has, on average, an impaired replication capacity relative to that of an otherwise similar population of viruses lacking the property. The method steps comprise: detecting whether the reverse transcriptase (RT) encoded by said HIV-1 exhibits the presence or absence of a mutation associated with impaired replication capacity. The mutation occurs at position 98, 100, 101, 103, 106, 108, 179, 181, 188, 190, 225 or 236 (not mutation P236L) in said reverse transcriptase. (The reference amino acid sequence for the reverse transcriptase is from HIV NL4-3, Genbank AF324493, see page 12 of the specification.) Specific substitution mutations are A98G, L100I, K101E, K103N, V106A, V106I, V106M, Y181C, Y188A, Y188C, Y188H, Y188L, G190A, G190C, G190E, G190T, G190V, G190Q, G190S, G190V, P236L and P225H. The mutation confers resistance to a non-nucleoside reverse transcriptase inhibitor, such as nevirapine,

delavirdine or efavirenz. Also claimed is a method for determining whether a subject has an HIV-1 with an increased likelihood of having an impaired replication capacity. The subject is undergoing or has undergone prior treatment with an antiviral drug. Also claimed are combinations of mutations that include P236L and K103N.

Nijhuis discloses the implications of antiretroviral resistance on viral fitness. Viral fitness is a synonym for replication capacity (page 23, introduction section). *In-vivo* drug resistance mutations on replication potential for HIV-1 in the presence of non-nucleoside reverse transcriptase inhibitors such as delavirdine include 103N (see Table 1, page 24, and page 25, first column, second full paragraph). Nijhuis teaches that the K103N mutation has a reducing effect on replicative capacity. Nijhuis also discloses that P236L is a NNRTI *in vivo* mutation that reduces replication capacity (Table 1). Given that Nijhuis discloses that the P236L and K103N mutations reduce replicative capacity and is an *in vivo* mutation that occurs after a single dose of NNRTI, the claimed methods are anticipated.

4. Claims 10 and 13-19 rejected under 35 U.S.C. 103(a) as being unpatentable over Nijhuis in view of Whitcomb (WO 99/61658). The claims are drawn to a method for determining whether an HIV-1 has an increased likelihood of having an impaired replication capacity. The method comprises detecting presence or absence of a mutation associated with impaired replication capacity at at least 2 and up to 12 amino acid positions. Specifically, the combination of mutations is P236L, K103N and Y181C. In some embodiments, the mutation cannot be P236L. The teachings of Nijhuis are summarized above. Nijhuis is silent on mutations of more than three positions relating to NNRTIs.

However, Whitcomb discloses means and methods for monitoring non-nucleoside reverse transcriptase inhibitor anti-retroviral therapy, specifically HIV therapy (abstract). Whitcomb discloses substitution mutations in HIV-1 reverse transcriptase at codons 101, 103 and/or 109 that correlate with changes in delavirdine, nevirapine and efavirenz susceptibility (page 12, lines 4-25). Also taught is that mutations at codons 106, 189, 181 and/or 227 of HIV-1 reverse transcriptase result in decreased susceptibility to delavirdine, nevirapine and efavirenz. Another embodiment of Whitcomb's invention is that a mutation at codon 190 (G190A) either alone or in combination with a mutation at codon 130 (K103N) of HIV-1 RT correlates with resistance to antiretroviral therapy (page 14, lines 29-34). Another embodiment of Whitcomb's invention is that a mutation at codon 236 (P236L) either alone or in combination with mutations at other codons including 103 (K103(N) and/or 181 (Y181C) of HIV RT correlates with resistance to antiretroviral therapy (see description of figures 5 and 6, pages 22-23). Other mutations include 225H (page 41, lines 13-15).

It would have been obvious to use the mutations taught by Whitcomb in Nijhuis' method. One would have been motivated to incorporate Whitcomb's additional mutations into Nijhuis' method because Nijhuis suggests that there is a relationship between viral replicative capacity and phenotypic resistance (page 27, column 1, second full paragraph). Nijhuis cites several examples including resistance to zidovudine wherein the virus harbors a single amino acid change or a combination of substitutions that have reduced replication capacity compared with the wild type (Table 1). One would have had a reasonable expectation of success that the detection of other mutations such as those taught by Whitcomb would have been predictive of viral fitness because some of the mutations are the same (K103N, P236L, for example) as those

that are associated with both NNRTI resistance and viral fitness. Therefore, the invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of invention.

Conclusion

5. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
May 10, 2005